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(54) **TREATMENT OF CANCER WITH SOMATOSTATIN AND ANALOGS THEREOF.**

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Description

This invention relates to therapeutic peptides.

Somatostatin is a naturally occurring tetradecapeptide having the following amino acid sequence:

$$H\text{-}Ala^{1}\text{-}Gly^{2}\text{-}Cys^{3}\text{-}Lys^{4}\text{-}Asn^{5}\text{-}Phe^{6}\text{-}Phe^{7}\text{-}Trp^{8}\text{-}Lys^{9}\text{-}Thr^{10}\text{-}Phe^{11}\text{-}Thr^{12}\text{-}Ser^{13}\text{-}Cys^{14}\text{-}OH.$$

A number of somatostatin analogs exhibiting GH-release-inhibiting activity have been described in the literature, including analogs containing fewer than the naturally occurring fourteen amino acids. For example, Coy et al, US Patent No. 4,485,101, describes dodecapeptides having an N-terminal acetyl group, a C-terminal NH_2, D-Trp at position 6, and p-Cl-Phe at position 4. (Herein, when no designation of configuration is given, the L-isomer is intended.)

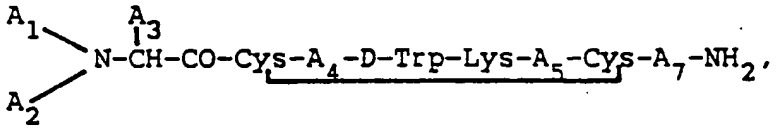
In general, the invention features use of somatostatin or an analog thereof containing six or more amino acids and having a similar tertiary structure and similar activity to natural somatostatin for the manufacture of a medicament for use in the treatment of small cell lung carcinoma in a human or other mammal wherein somatostatin or the analog thereof is in a form suitable for the administration of at least 25 µg/kg/day.

Preferably the cancer is characterized by the presence of a solid tumour. If slow growing (less than 0.25 mm/day increase), somatostatin or the analog thereof can be in a form suitable for administration of less than 250 µg/kg/day. If the tumour is fast growing, the somatostatin or analog thereof is preferably in a form suitable for administration of at least 250 µg/kg/day, more preferably at least 500 µg/kg/day.

In another aspect, the somatostatin or analog thereof is preferably in a form suitable for administration at the site of the tumour.

In preferred embodiments of both aspects of the invention, the somatostatin or analog thereof is in a form suitable for continuous administration, carried out using pump means or sustained release means. Preferably, in both methods, the somatostatin analog has a four or greater amino acid sequence homologous with the core region of somatostatin. (The core region is made up of the amino acids at positions 4, 5, 6, 7, 8, 9 and 10). More preferably, the somatostatin analog has a six or seven amino acid sequence homologous with the core region of somatostatin. Preferably, the somatostatin analog has D-Trp at position 8.

One class of somatostatin analogs which are suitable in the cancer therapy method of the invention are octapeptides of the formula:



wherein each A_1 and A_2, independently, is H, C_{1-12} alkyl, C_{7-10} phenylalkyl, R_1CO (where R_1 is C_{1-20} alkyl, C_{3-20} alkenyl, C_{3-20} alkynyl, phenyl, naphthyl, or C_{7-10} phenylalkyl), or R_2OCO (where R_2 is C_{1-10} alkyl or C_{7-10} phenylalkyl), provided that when one of A_1 or A_2 is R_1CO or R_2OCO, the other must be H; A_3 is CH_2-A_6 (where A_6 is pentafluorophenyl, naphthyl, pyridyl, phenyl, or o-, m-, or, more preferably, p-substituted phenyl, where the substituent is a halogen, NH_2, NO_2, OH, or C_{1-3} alkyl); A_4 is o-, m-, or, more preferably, p-substituted X-Phe (where X is a halogen, H, NH_2, NO_2, OH, or C_{1-3} alkyl), pentafluoro-Phe, or β-Nal; A_5 is Thr, Ser, Phe, Val, α-aminobutyric acid, or Ile, provided that when A_3 is phenyl, A_1 is H, and A_2 is H, A_5 cannot be Val; and A_7 is Thr, Trp, or β-Nal; or a pharmaceutically acceptable salt thereof.

In the formula given above, the configuration of the molecule at the carbon atom to which A_3 is bonded is not given, to indicate that the amino acid residue of which A_3 is a substituent can have the D-or L-configuration.

Preferred compounds of the above-described formula include

D-ß-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2; D-Phe-Cys-Tyr-D-Trp-Lys-α-Aminobutyric acid-Cys-Thr-NH_2; pentafluoro-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2; N-Ac-D-ß-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2; D-ß-Nal-Cys-pentafluoro-Phe-D-Trp-Lys-Val-Cys-Thr-NH_2; D-ß-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-ß-Nal-NH_2; D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-ß-Nal-NH_2; D-ß-Nal-Cys-Tyr-D-Trp-Lys-α-aminobutyric acid-Cys-Thr-NH_2; D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-α-aminobutyric acid-Cys-Thr-NH_2; and acetyl-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-α-aminobutyric acid-Cys-Thr-NH_2.

The compounds which have an aromatic, lipophilic N-terminus have the further advantage of long-lasting in vivo activity.

A therapeutically effective amount of the therapeutic compound and a pharmaceutically acceptable carrier substance, e.g. magnesium carbonate, lactose, or a phospholipid with which the therapeutic compound can form a micelle, together can form a therapeutic composition, e.g. a pill, tablet, capsule, or liquid for oral administration to a patient, a spreadable cream, gel, lotion, or ointment for application to the skin of a patient in need of the compound, a liquid capable of being administered nasally as drops or spray, or a liquid capable of intravenous, parenteral, subcutaneous, or intraperitoneal administration. The most preferred carrier substance is mannitol. The pill, tablet or capsule can be coated with a substance capable of protecting the composition from the gastric acid in the patient's stomach for a period of time sufficient to allow the composition to pass undisintegrated into the patient's small intestine. The therapeutic composition can also be in the form of a biodegradable sustained release formulation for intramuscular administration or, more preferably, administration at the site of a tumor. For maximum efficacy, zero order release is desired. Zero order release can be obtained using an implantable or external pump, e.g., an Infusaid™ pump (Infusaid Corp., Massachusetts), to administer the therapeutic composition. In addition, the therapeutic composition can be administered in the form of an oil emulsion or dispersion in conjunction with a lipophilic salt such as a pamoic acid.

The invention provides effective cancer therapy, at dosages which can be much higher, e.g., 30 times or greater higher, than the amounts of the compounds which are effective to significantly inhibit release of growth hormone, and yet these high dosages do not cause significant toxic side effects.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof.

Figs. 1-4 are graphs illustrating the effect of a somatostatin analog (referred to in the drawings as "BIM23014C") on the growth of tumors.

Suitable compounds for cancer treatment are somatostatin or the somatostatin analogs described in the Summary of the Invention, above. Examples are the following analogs, which have been shown to bind to tumor receptors of human small cell lung carcinoma (cell line NCI H69): (binding to such receptors, although possibly related to antitumoral activity, is not necessarily required for such activity.)

D-ß-Nal

-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2;

D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Nal;

D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2; and

D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2.

("Nal" refers to naphthylalanine.)

Other suitable somatostatin analogs include the analogs described in Veber et al. (1984) Life Sciences, 34: 1371-78; Bauer et al., U.S. 4,395,403; Bauer et al., U.S. 4.435,385; Sandrin et.al., U.S. 4,291,022; Coy et al., U.S. 4,485,101, described above; and Cai et al. (1986) P.N.A.S. U.S.A. 83, 1896-1900.

The synthesis of one octapeptide analog of somatostatin follows. Other analogs can be prepared by making appropriate modifications, within the ability of someone of ordinary skill in this field, of the following synthetic method.

The first step in the preparation of

D-ß-naphthylalanine-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr- NH_2

was the preparation of the intermediate tert-butyloxycarbonyl-D-β-naphthylalanine-S-methylbenzyl-Cys-Tyr-D-Trp-N'-benzyloxycarbonyl-Lys-Val-S-methylbenzyl-Cys-O-benzyl-Thr-benzyhydrylaminine resin, as follows.

Benzhydrylamine-polystyrene resin (Vega Biochemicals, Inc.) in the chloride ion form was placed in the reaction vessel of a Beckman 990B peptide synthesizer programmed to perform the following reaction cycle: (a) methylene chloride; (b) 33% trifluoroacetic acid in methylene chloride (2 times for 1 and 25 min each); (c) methylene chloride; (d) ethanol; (e) methylene chloride; (f) 10% triethylamine in chloroform.

The neutralized resin was stirred with Boc-O-benzyl-threonine and diisopropylcarbodiimide (1.5 mmole each) in methylene chloride for 1 h and the resulting amino acid resin was then cycled through steps (a) to (g) in the above wash program. The following amino acids (1.5 mmole) were then coupled successively by the same procedure: Boc-S-methylbenzyl-Cys, Boc-Val, Boc-Ne-benzyloxycarbonyl-lysine, Boc-D-Trp, Boc-Tyr, Boc-S-methylbenzyl-Cys, Boc-D-β-naphthylalanine.

The resin was washed and dried and then mixed with anisole (4 ml) and anhydrous hydrogen fluoride (36 ml) at 0°C and stirred for 45 min. (one can also use thioanisole, trifluoroacetic acid, and trifluoromethane sulfonic acid at a ratio of 1:90:9, for 6h). Excess hydrogen fluoride was evaporated rapidly under a stream of dry nitrogen and free peptide precipitated and washed with ether. The crude peptide was then dissolved in 800 ml of 90% acetic acid to which was added I_2 in methanol until a permanent brown color was present. The solution was then stirred for 1 h before removing the solvent in vacuo. The resulting oil was dissolved in a minimum volume of 50% acetic acid and eluted on a column (2.5 X 100 mm) of Sephadex G-25. Fractions containing a major component by uv absorption and thin layer chromatography were then pooled, evaporated to a small volume, and applied to a column (2.5 X 50 cm) of Whatman LRP-I octadecylsilane (15-20 μM).

The column was eluted with a linear gradient of 10-50% acetonitrile in 0.1% trifluoroacetic acid in water. Fractions were examined by thin layer chromatography and analytical high performance liquid chromatography and pooled to give maximum purity and if desired, a different salt prepared, e.g., acetate or phosphate. Repeated lyophilization of the solution from water gave 170 mg of the product as a white, fluffy powder.

The product was found to be homogeneous by Hplc and Tlc. Amino acid analysis of an acid hydrolysate confirmed the composition of the octapeptide.

The octapeptides of the invention having the formulae

pentafluoro-D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2, D-Phe-Cys-Tyr-D-Trp- Lys-α-aminobutyric acid-Cys-Thr-NH_2,

N-Ac-D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2,

D-β-Nal-Cys pentafluoro-Phe-D-Trp-Lys-Val-Cys-Thr-NH_2, D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2, D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-β-Nal-NH_2; D-β-Nal-Cys-Tyr-D-Trp-Lys-α-aminobutyric acid-Cys-Thr-NH_2; D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-α-aminobutyric acid-Cys- Thr-NH_2; and acetyl-D-p-Cl-Phe-Cys-Tyr-D-Trp-Lys-α-aminobutyric acid-Cys-Thr-NH_2

were made according to methods analogous to those described above.

The medicaments manufactured provide effective treatment for cancers, particularly solid tumor carcinomas such as small cell lung carcinoma. Other cancers which can be treated include bone, cartilage, pancreas (endocrine and exocrine), prostate, and breast cancers.

The above-described compounds, and somatostatin and its hexapeptide or higher analogs generally, are useful in the treatment of cancer when administered as described above. The anti-cancer agent is preferably administered directly to the site of the cancerous tumor; indirect, e.g., oral, administration is not as preferred because it requires higher dosages. The agents generally have on the order of a 6 hour lifetime in vivo, and therefore four treatments per day are preferred if non-continuous administration is used, e.g., intravenous injections, as are generally necessary for inaccessible tumors.

The octapeptide somatostatin analog

D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2

was tested for its ability to inhibit the proliferation of cells of tumors; the results are given in Figs. 1-4.

Figs. 1 and 2 show the effect of the analog on human small cell carcinoma (line NCI-H69), which is a fast growing tumor (0.33 mm/day), implanted in athymic mice. The analog, when administered at the site of the tumor, exhibited a marked effect on the tumor.

Fig. 3 shows the effect of the same analog on the rapidly growing (0.77 mm/day) cancer human oat cell carcinoma (line LX-I).

Fig. 4 shows the effect of the same analog on a slow growing (0.19 mm/day) rat prostate tumor.

Claims

1. Use of somatostatin or an analog thereof containing six or more amino acids and having a similar tertiary structure and similar activity to natural somatostatin for the manufacture of a medicament for use in the treatment of small cell lung carcinoma in a human or other mammal wherein somatostatin or the analog thereof is in a form suitable for the administration of at least 25 µg/kg/day.

2. Use of somatostatin or an analog thereof containing six or more amino acids and having a similar tertiary structure and similar activity to natural somatostatin for the manufacture of a medicament for use in the treatment of small cell lung carcinoma in a human or other mammal wherein somatostatin or the analog thereof is in a form suitable for the administration of at least 250 µg/kg/day.

3. Use of somatostatin or an analog thereof containing six or more amino acids and having a similar tertiary structure and similar activity to natural somatostatin for the manufacture of a medicament for use in the treatment of small cell lung carcinoma in a human or other mammal wherein somatostatin or the analog thereof is in a form suitable for the administration of at least 500 µg/kg/day.

4. Use of somatostatin or an analog thereof containing six or more amino acids and having a similar tertiary structure and similar activity to natural somatostatin for the manufacture of a medicament for use in the treatment of small cell lung carcinoma in a human or other mammal wherein somatostatin or the analog thereof is in a form suitable for direct administration to the site of said carcinoma.

5. Use of somatostatin or an analog thereof containing six or more amino acids and having a similar tertiary structure and similar activity to natural somatostatin for the manufacture of a medicament for use in the treatment of small cell lung carcinoma in a human or other mammal wherein somatostatin or the analog thereof is in a form suitable for direct administration to the site of said carcinoma at a dosage rate of at least 25 µg/kg/day.

6. Use of somatostatin or an analog thereof containing six or more amino acids and having a similar tertiary structure and similar activity to natural somatostatin for the manufacture of a medicament for use in the treatment of small cell lung carcinoma in a human or other mammal wherein somatostatin or the analog thereof is in a form suitable for direct administration to the site of said carcinoma at a dosage rate of at least 250 µg/kg/day.

7. Use of somatostatin or an analog thereof containing six or more amino acids and having a similar tertiary structure and similar activity to natural somatostatin for the manufacture of a medicament for use in the treatment of small cell lung carcinoma in a human or other mammal wherein somatostatin or the analog thereof is in a form suitable for continual administration to said carcinoma by pump means or sustained release means.

8. Use of a somatostatin analog as claimed in any preceding claim, wherein the analog has a four or greater amino acid sequence homologous with the core region of somatostatin.

9. Use of a somatostatin analog as claimed in Claim 8, wherein the analog has a six or seven amino acid sequence homologous with the core region of somatostatin.

10. Use of a somatostatin analog as claimed in any preceding claim, wherein the analog has D-Trp at position 8.

Patentansprüche

1. Verwendung von Somatostatin oder eines Analogons davon, das sechs oder mehr Aminosäuren enthält, und eine ähnliche Tertiärstruktur und ähnliche Aktivität wie natürliches Somatostatin besitzt, zur Herstellung eines Medikaments zur Verwendung bei der Behandlung des Alveolarzellkarzinoms beim Menschen oder einem anderen Säuger, bei der Somatostatin oder dessen Analogon in einer zur Verabreichung von wenigstens 25 µg/kg/Tag geeigneten Form vorliegt.

2. Verwendung von Somatostatin oder eines Analogons davon, das sechs oder mehr Aminosäuren enthält und eine ähnliche Tertiärstruktur und eine ähnliche Aktivität wie natürliches Somatostatin aufweist, zur Herstellung eines Medikaments zur Verwendung bei der Behandlung des Alveolarzellkarzinoms beim Menschen oder einem anderen Säuger, bei der Somatostatin oder dessen Analogon in einer zur Verabreichung von wenigstens 250 µg/kg/Tag geeigneten Form vorliegt.

3. Verwendung von Somatostatin oder eines Analogons davon, das sechs oder mehr Aminosäuren enthält und eine ähnliche Tertiärstruktur und eine ähnliche Aktivität wie natürliches Somatostatin aufweist, zur Herstellung eines Medikaments zur Verwendung bei der Behandlung des Alveolarzellkarzinoms beim Menschen oder einem anderen Säuger, bei der Somatostatin oder dessen Analogon in einer zur Verabreichung von wenigstens 500 µg/kg/Tag geeigneten Form vorliegt.

4. Verwendung von Somatostatin oder eines Analogons davon, das sechs oder mehr Aminosäuren enthält und eine ähnliche Tertiärstruktur und eine ähnliche Aktivität wie natürliches Somatostatin aufweist, zur Herstellung eines Medikaments zur Verwendung bei der Behandlung des Alveolarzellkarzinoms beim Menschen oder einem anderen Säuger, bei der Somatostatin oder dessen Analogon in einer Form vorliegt, die zur direkten Verabreichung auf die Stelle des genannten Karzinoms geeignet ist.

5. Verwendung von Somatostatin oder eines Analogons davon, das sechs oder mehr Aminosäuren enthält und eine ähnliche Tertiärstruktur und eine ähnliche Aktivität wie natürliches Somatostatin aufweist, zur Herstellung eines Medikaments zur Verwendung bei der Behandlung des Alveolarzellkarzinoms beim Menschen oder einem anderen Säuger, bei der Somatostatin oder dessen Analogon in einer Form vorliegt, die zur direkten Verabreichung auf die Stelle des genannten Karzinoms in einer Dosierungskonzentration von wenigstens 25 µg/kg/Tag geeignet ist.

6. Verwendung von Somatostatin oder eines Analogons davon, das sechs oder mehr Aminosäuren enthält und eine ähnliche Tertiärstruktur und eine ähnliche Aktivität wie natürliches Somatostatin aufweist, zur Herstellung eines Medikaments zur Verwendung bei der Behandlung des Alveolarzellkarzinoms beim Menschen oder einem anderen Säuger, bei der Somatostatin oder dessen Analogon in einer Form vorliegt, die zur direkten Verabreichung auf die Stelle des genannten Karzinoms in einer Dosierungskonzentration von wenigstens 250 µg/kg/Tag geeignet ist.

7. Verwendung von Somatostatin oder eines Analogons davon, das sechs oder mehr Aminosäuren enthält und eine ähnliche Tertiärstruktur und eine ähnliche Aktivität wie natürliches Somatostatin aufweist, zur Herstellung eines Medikaments zur Verwendung bei der Behandlung des Alveolarzellkarzinoms beim Menschen oder einem anderen Säuger, bei der Somatostatin oder dessen Analogon in einer Form vorliegt, die zur kontinuierlichen Verabreichung auf das genannte Karzinom durch ein Pumpenmittel oder ein Mittel zur verzögerten Freizetzung geeignet ist.

8. Verwendung eines Somatostatin-Analogons nach einem der vorgenannten Ansprüche, bei der das Analogon eine Sequenz von vier Aminosäuren oder mehr aufweist, die zu der Kernregion von Somatostatin homolog ist.

9. Verwendung eines Somatostatin-Analogons nach Anspruch 8, bei der das Analogon eine Sequenz von sechs oder sieben Aminosäuren aufweist, die zu der kernregion von Somatostatin homolog ist.

10. Verwendung eines Somatostatin-Analogons nach einem der vorgenannten Ansprüche, bei der das Analogon in Position 8 D-Trp aufweist.

Revendications

1. Utilisation de la somatostatine ou d'un de ses analogues contenant au moins six amino-acides et présentant une structure tertiaire et une activité semblables à celles de la somatostatine naturelle, pour la fabrication d'un médicament destiné à être utilisé dans le traitement du carcinome du poumon à petites cellules, chez l'homme ou chez un autre mammifère, dans lequel la somatostatine ou son analogue se trouve sous une forme appropriée pour l'administration d'au moins 25 µg/kg/jour.

2. Utilisation de la somatostatine ou d'un de ses analogues contenant au moins six amino-acides et présentant une structure tertiaire et une activité semblables à celles de la somatostatine naturelle, pour la fabrication d'un médicament destiné à être utilisé dans le traitement du carcinome du poumon à petites cellules, chez l'homme ou chez un autre mammifère, dans lequel la somatostatine ou son analogue se trouve sous une forme appropriée pour l'administration d'au moins 250 µg/kg/jour.

3. Utilisation de la somatostatine ou d'un de ses analogues contenant au moins six amino-acides et présentant une structure tertiaire et une activité semblables à celles de la somatostatine naturelle, pour la fabrication d'un médicament destiné à être utilisé dans le traitement du carcinome du poumon à petites cellules, chez l'homme ou chez un autre mammifère, dans lequel la somatostatine ou son analogue se trouve sous une forme appropriée pour l'administration d'au moins 500 µg/kg/jour.

4. Utilisation de la somatostatine ou d'un de ses analogues contenant au moins six amino-acides et présentant une structure tertiaire et une activité semblables à celles de la somatostatine naturelle, pour la fabrication d'un médicament destiné à être utilisé dans le traitement du carcinome du poumon à petites cellules, chez l'homme ou chez un autre mammifère, dans lequel la somatostatine ou son analogue se trouve sous une forme appropriée pour une administration directe sur le site dudit carcinome.

5. Utilisation de la somatostatine ou d'un de ses analogues contenant au moins six amino-acides et présentant une structure tertiaire et une activité semblables à celles de la somatostatine naturelle, pour la fabrication d'un médicament destiné à être utilisé dans le traitement du carcinome du poumon à petites cellules, chez l'homme ou chez un autre mammifère, dans lequel la somatostatine ou son analogue se trouve sous une forme appropriée pour une administration directe sur le site dudit carcinome, à un dosage d'au moins 25 µg/kg/jour.

6. Utilisation de la somatostatine ou d'un de ses analogues contenant au moins six amino-acides et présentant une structure tertiaire et une activité semblables à celles de la somatostatine naturelle, pour la fabrication d'un médicament destiné à être utilisé dans le traitement du carcinome du poumon à petites cellules, chez l'homme ou chez un autre mammifère, dans lequel la somatostatine ou son analogue se trouve sous une forme appropriée pour l'administration directe sur le site dudit carcinome à un dosage d'au moins 250 µg/kg/jour.

7. Utilisation de la somatostatine ou d'un de ses analogues contenant au moins six amino-acides et présentant une structure tertiaire et une activité semblables à celles de la somatostatine naturelle, pour la fabrication d'un médicament destiné à être utilisé dans le traitement du carcinome du poumon à petites cellules, chez l'homme ou chez un autre mammifère, dans lequel la somatostatine ou son analogue se trouve sous une forme appropriée pour l'administration continue, sur ledit carcinome, à l'aide d'un dispositif à pompe ou d'une forme à libération prolongée.

8. Utilisation d'un analogue de la somatostatine tel que revendiquée dans l'une quelconque des revendications précédentes, dans laquelle l'analogue comporte une séquence d'au moins quatre amino-acides, homologue avec la partie centrale de la somatostatine.

9. Utilisation d'un analogue de la somatostatine tel que revendiquée dans la revendication 8, dans laquelle cet analogue comporte une séquence de six ou de sept amino-acides homologue avec la partie centrale de la somatostatine.

10. Utilisation d'un analogue de la somatostatine tel que revendiquée dans l'une quelconque des revendications précédentes, caractérisée par le fait que cet analogue comporte un D-Trp en position 8.

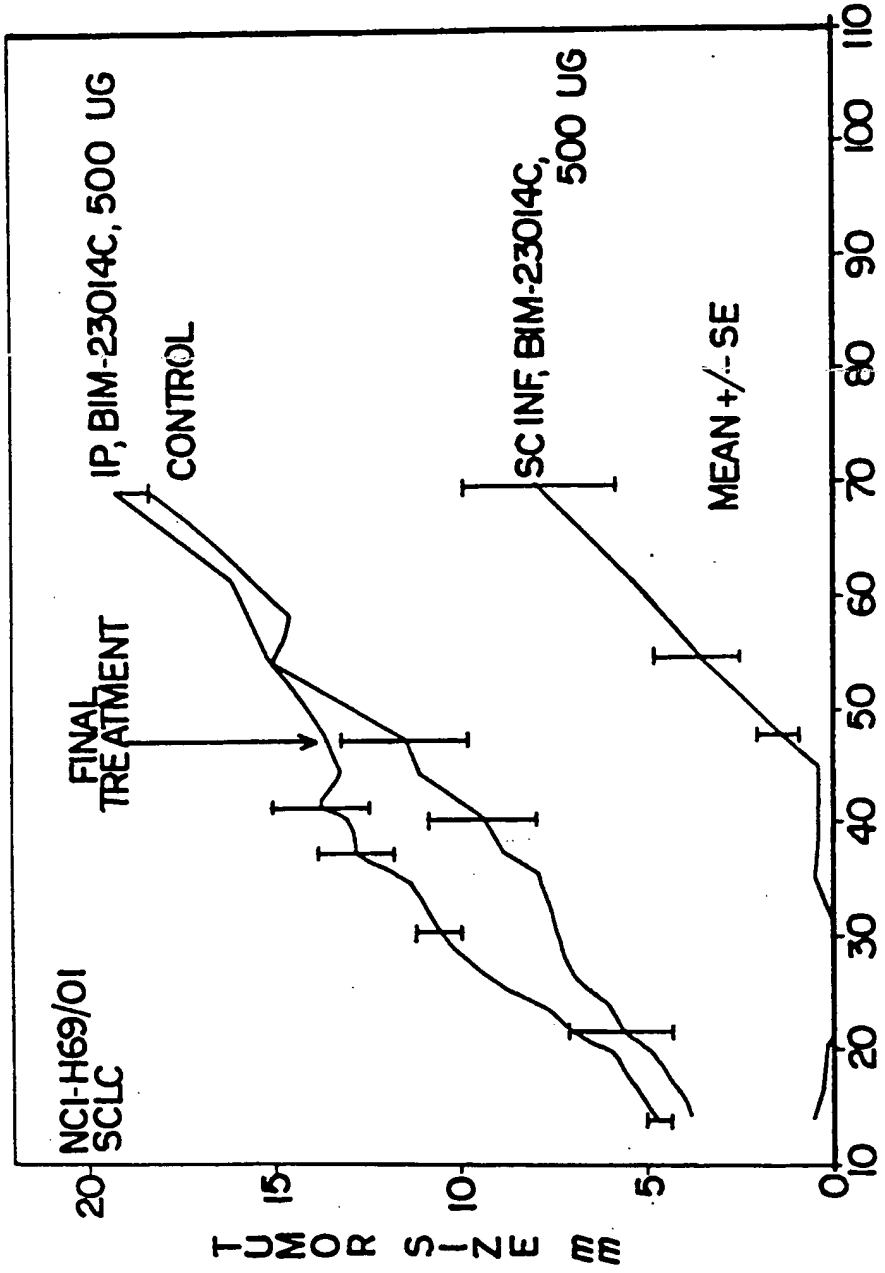

NCI-H69/01
SCLC
FINAL
TREATMENT
IP, BIM-23014C, 500 UG
CONTROL
SC INF, BIM-23014C,
500 UG
MEAN +/- SE
TUMOR SIZE mm
DAYS POST TUMOR IMPLANTATION
0
5
10
15
20
10
20
30
40
50
60
70
80
90
100
110

FIG.1

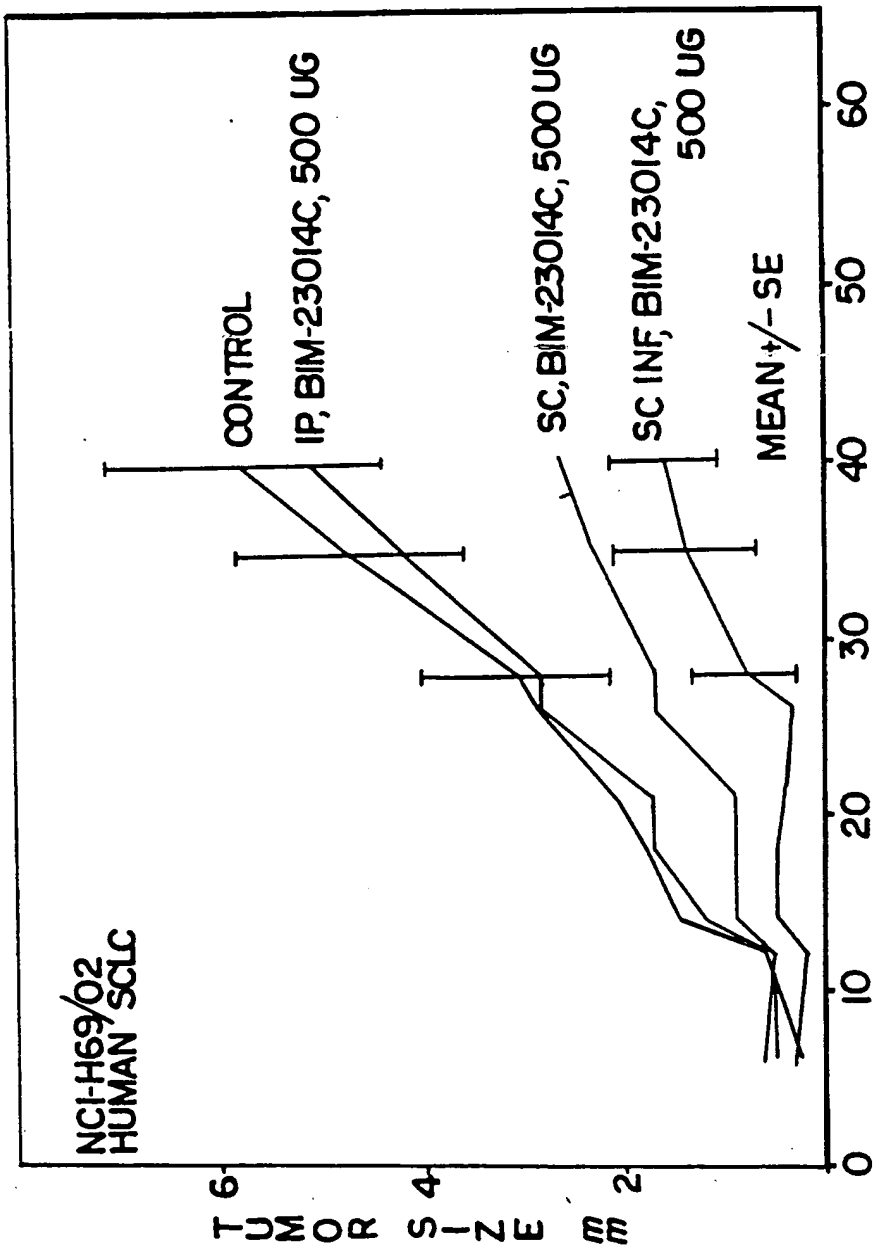

NCI-H69/02
HUMAN SCLC
CONTROL
IP, BIM-23014C, 500 UG
SC, BIM-23014C, 500 UG
SC INF, BIM-23014C, 500 UG
MEAN +/- SE
TUMOR SIZE m^2
0
2
4
6
10
20
30
40
50
60
DAYS POST TUMOR IMPLANTATION

FIG.2

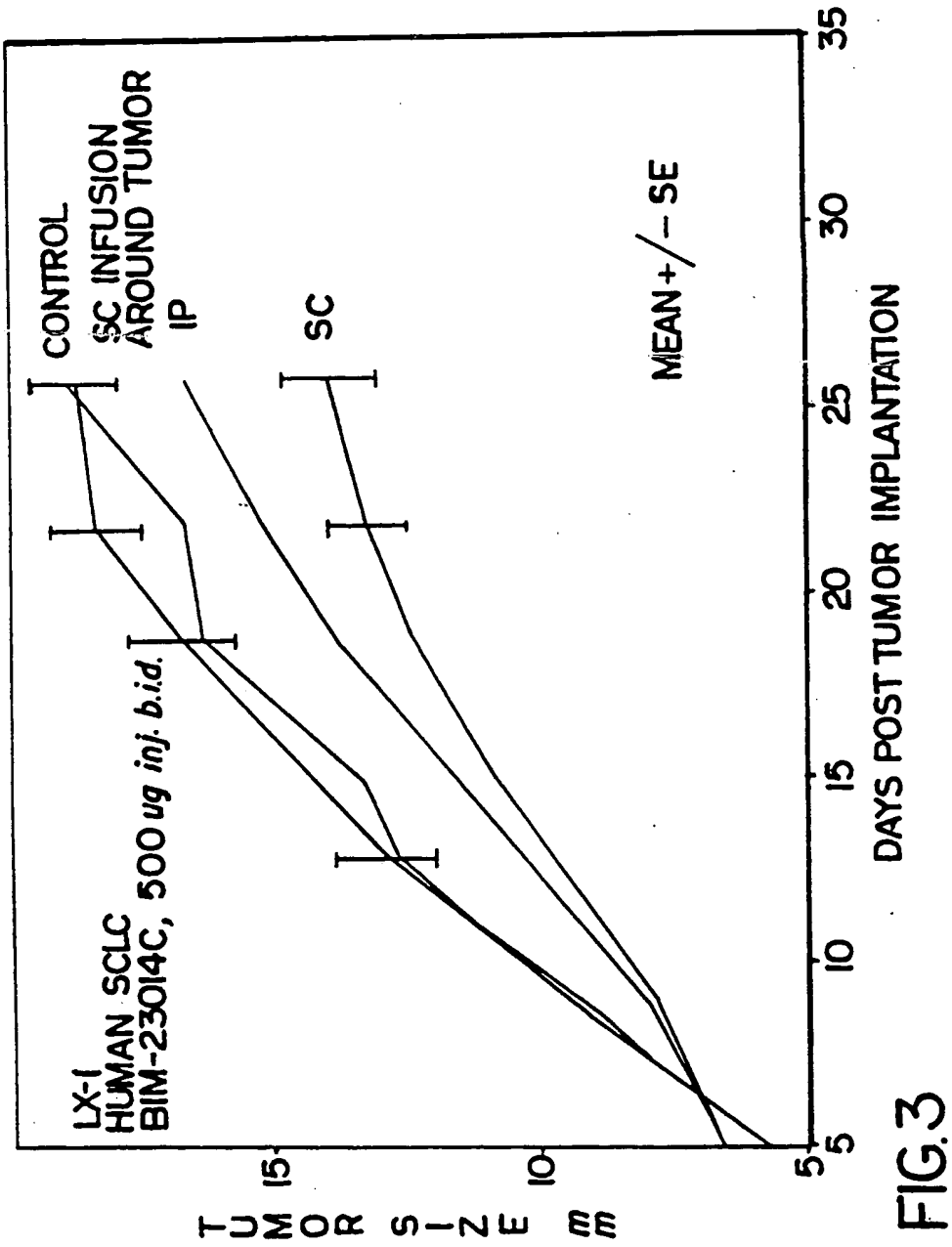

LX-1
HUMAN SCLC
BIM-23014C, 500 ug inj. b.i.d.
CONTROL
SC INFUSION
AROUND TUMOR
IP
SC
MEAN +/- SE
TUMOR SIZE mm
5
10
15
5
10
15
20
25
30
35
DAYS POST TUMOR IMPLANTATION

FIG.3

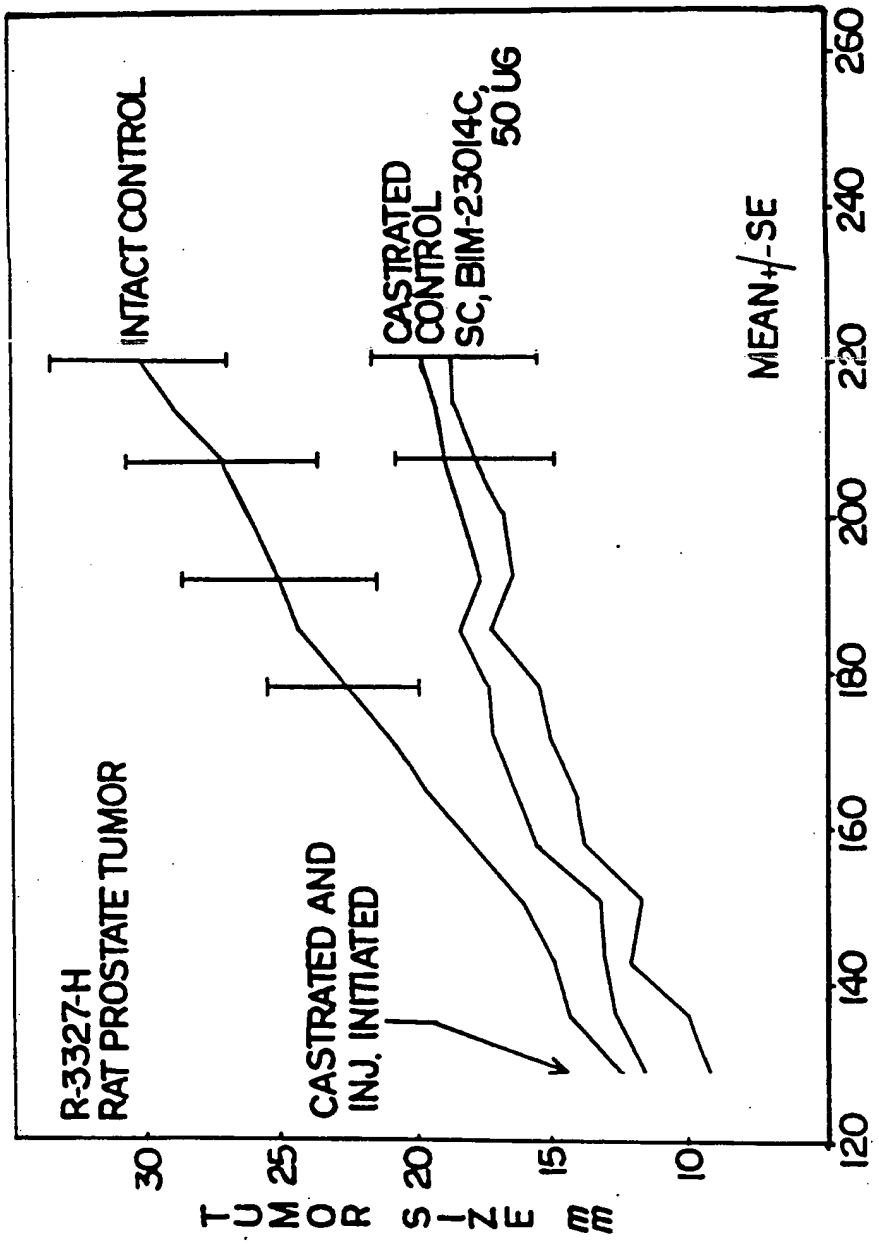

R-3327-H
RAT PROSTATE TUMOR
INTACT CONTROL
CASTRATED AND
INJ. INITIATED
CASTRATED
CONTROL
SC, BIM-23014C,
50 UG
MEAN+/-SE
TUMOR SIZE mm
30
25
20
15
10
120
140
160
180
200
220
240
260
DAYS POST TUMOR IMPLANTATION

FIG.4